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Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

| EXAMINER | |
|---|---|
| CHONG, KIMBERLY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/618,408 | EINAT ET AL. | |
| | Examiner | Art Unit | |
| | Kimberly Chong | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3,7,10-22 and 24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6,8,9 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

Claims 1-26 are pending in the instant application. Claims 1, 2, 4, 5, 6, 8, 9 and 23 are currently under examination. Claims 3, 7, 12-22 and 24-26 are withdrawn.

### *Election/Restrictions*

Claims 3, 7 and 10-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/20/2005.

Applicant has added claims 23-26 and asserts the newly added claims correspond to the subject matter of the elected invention. Newly added claim 23 is drawn to the elected invention, however claims 24-26 are drawn to a different invention.

Newly submitted claims 24-26 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 24-26 are drawn to a method of treating an apoptosis-related disease comprising administering an expression inhibitor of WWP1 wherein the inhibitor is a siRNA. The subject matter of the newly added claims is divergent and non-coextensive with the elected invention and a search for one would not necessarily reveal art against the other. It is therefore a burden to search these inventions in a single application because the elected invention requires a search of a method of treating using

an antisense molecule whereas the newly submitted claims 24-26 requires a search of a method of treating using a siRNA which is a different molecule with a different mechanism.

Thus, newly submitted claims 24-26 are withdrawn as being drawn to a non-elected invention

Applicant argues that there is no search burden to examine groups I-VIII together because "[a]ny search for treating an apoptosis-related disease using an inhibitor of WWP1 polypeptide will turn up other inhibitors of the WWP1 polypeptide, other methods of treatment, and methods of using the WWP1 polypeptide."

Groups II and IV, claims 1, 2, 4, 5, 6, 8, 9 and 23, will be examined together because a method of treatment using an antisense inhibitor of WWP1 could reveal art for a method of treatment using an antisense inhibitor of WWP1 and a chemotherapeutic agent. However, the subject matter of groups I, III and V-VIII are divergent and non-coextensive because a search for one wound not necessarily reveal art against the other. For instance, a search for a method of treatment using an antisense molecule would not reveal art for a method of treatment using an antibody. Furthermore, a search for a method of treatment using an antisense molecule would not necessarily reveal art for a process for determining the WWP1 polypeptide of polynucleotide levels in a cell or a process for screening compounds that promote apoptosis in a cell. Therefore, the restriction of groups I, III and V-VIII is proper because it is a search burden to search these inventions in a single application.

**The restriction is deemed FINAL.**

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8, 9 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "for potentiating a chemotherapeutic treatment" in the first and second line. There is insufficient antecedent basis for this limitation in the claim.

Claim 23 recites the limitation "wherein the AS fragment comprising consecutive nucleotides having the sequence set forth in SEQ ID NO:3". There is insufficient antecedent basis for this limitation in the claim.

Claim 23 is recites the limitation "wherein the AS fragment comprising consecutive nucleotides having the sequence set forth in SEQ ID NO:3". This is an incomplete sentence. It is unclear what is meant by this sentence. For example, is the AS fragment targeted to a gene encoding WWP1? Does the AS fragment inhibit the polypeptide encoded by a WWP1 gene?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 6, 8, 9 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are broadly drawn to a method of treatment of any apoptosis-related disease in a subject comprising administering any inhibitor of the WWP1 polypeptide, in a dosage sufficient to inhibit WWP1 and thereby treat a subject. There is no specific description provided of an inhibitor targeted to any version of WWP1 which will bind to WWP1, inhibit the expression of WWP1 and provide treatment of any apoptosis-related disease in a subject.

The specification as filed only discloses one antisense fragment (SEQ ID NO: 3) which only teaches an increased sensitivity to apoptosis when transfected into cells (see Example II). The antisense fragment (SEQ ID NO:3) does not provide information regarding the structure of other inhibitors that will allow one skilled in the art to practice the claimed invention, namely inhibit WWP1 and treat any apoptosis-related disease in a subject.

The scope of the claimed invention is so broad that the skilled artisan would not be able to envisage the entire genus claimed of inhibitors that would inhibit any WWP1 and further provide treatment to any apoptosis-related disease such that the skilled artisan would recognize that the applicant was in possession of the claimed invention at the time of filing. Not only do the claims read on any WWP1 target, but additionally the skilled artisan would not be able to envisage which inhibitor would inhibit the WWP1 polypeptide and treat any apoptosis-related disease without undue experimentation.

Additionally, the prior art teaches several known nucleic acid sequences of WWP1 originating from human, mouse or C. elegans (see Huang et al. Gene 2000). The general knowledge in the prior art concerning WWP1 nucleic acid sequences does not provide any indication of what structure to what WWP1 will provide treatment of any apoptosis-related disease. Although the specification teaches one antisense compound (SEQ ID NO. 3), the specification as filed nor the prior art provide a description as to what other inhibitor for which version of WWP1 will provide treatment of an apoptosis-related disease.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

MPEP 2163 states in part, "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which

peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")

Thus, the instantly claimed invention cannot be said to have been adequately described in a way that would convey with reasonable clarity to those skilled in the art that, as of the filling date, applicant was in possession of the claimed invention because the specification, while providing information on one antisense fragment inhibitor (SEQ ID NO. 3), does not provide any other information or guidance as to what inhibitor for which version of WWP1 will provide treatment of an apoptosis-related disease in a subject.

Claims 1, 2, 4, 5, 6, 8, 9 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method of treatment of an apoptosis-related disease in a subject comprising administering an inhibitor of the WWP1 polypeptide and further wherein the inhibitor is an antisense fragment.

The specification as filed discloses that HeLa cells transfected *in vitro* with an antisense fragment targeted to WWP1 are more sensitive to FAS mediated apoptosis (see example II of the specification). Further, the specification as filed discloses that introduction of the full length WWP1 cDNA into cells, *in vitro*, caused protection from FAS mediated apoptosis (see example II of the specification). The specification as filed does not teach that because of administration

of an antisense compound targeted to WWP1, WWP1 is inhibited *in vitro* or *in vivo* and therefore treatment of any apoptosis-related disease in a subject is provided.

There is no guidance in the specification as filed that teaches how to target the claimed antisense compound to human cells or tissues, inhibit the expression of WWP1 and further provide treatment for any apoptosis-related disease. Although the specification discloses FAS mediated apoptosis after transfection of an antisense inhibitor of WWP1 *in vitro*, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable.

The following factors have been considered in the analysis of enablement: (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the level of one of ordinary skill, (5) the level of predictability in the art, (6) the amount of direction provided by the inventor, (7) the existence of working examples, (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claimed breadth of claims 1, 2, 4, 5, 6, 8, 9 and 23 encompass methods of treating a broad range of apoptosis-related diseases in different tissues by use of an antisense targeted to WWP1 *in vivo*. Although the specification teaches FAS mediated apoptosis in cells *in vitro* after transfection with an antisense targeted to WWP1 (see example II), this guidance is not sufficient to resolve the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by the instantly claimed methods.

The references cited herein illustrate the state of the art for therapeutic *in vivo* applications using antisense compounds. Branch stresses that "because it is very difficult to predict what portions of an RNA molecule will be accessible in vivo, effective antisense

molecules must be found empirically by screening a large number of candidates for their ability to act inside cells" (TIB 23: 45-50 1998). Green *et al.* states that "[i]t is clear from the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense [oligonucleotides] can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established. In addition, toxicity in humans appears more problematic than might be predicted based on preclinical studies in rodents. Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects" (Antisense Therapy in Human Disease; Vol. 191, No. 1 2000, pg 103 column 2).

The problems with efficient delivery of antisense oligonucleotides to cells has been addressed by Jen *et al.*, who states that "[o]ne of the major limitations for the therapeutic use of AS-ODNS ...is the problem of delivery....presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable (Stem Cells 2000; 18:307-319 pg 315 column 2)." Jen *et al.* concludes that "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive (see p 315, second column)."

Additionally, Monia et al. (US Patent No. 6,258,601) illustrate the start of the art for antisense therapeutics by only demonstrating inhibition of WWP1 expression in cells *in vitro* after treatment with an antisense targeted to a gene encoding WWP1 (see Examples 15-16 and Table 1-2).

As outlined above, it is well known that there is a high level of unpredictability in the antisense art for therapeutic *in vivo* applications. The scope of the claims in view of the specification as filed together do not reconcile the unpredictability in the art to enable one of skill in the art to make and/or use the claimed invention, namely treatment of any apoptosis-related disease after administration of an antisense compound targeted to a gene encoding WWP1.

While one skilled in the art may be able to find an antisense fragment targeted to a gene encoding WWP1 and demonstrate inhibition of WWP1 in cells *in vitro* after treatment with the antisense fragment, the specification as filed does not teach how to administer any antisense fragment and further to treat an apoptosis-related disease by administration of the antisense fragment as claimed.

Crooke (Antisense Research and Application, Chapter 1, Springer-Verlag, New York. 1998) supports the difficulties of extrapolating from *in vitro* experiments and states on p. 3, paragraph 2, "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies [references omitted]."

In view of the unpredictability in the art of antisense-based therapy, as outlined above, the specification as filed does not provide adequate guidance that would show how one skilled in the art would practice the claimed invention without undue experimentation.

Given the teachings of the specification as discussed above, one skilled in the art would not know *a priori* whether introduction of antisense oligonucleotides *in vivo* by the broadly

disclosed methodologies of the instantly claimed invention, would result in successful inhibition of expression of a target gene. To practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to practice a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

## ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Kimberly Chong
Examiner
Art Unit 1635

SEAN McGARRY
PRIMARY EXAMINER